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Pentoxifylline for treating venous leg ulcers (Review)

Jull AB, Arroll B, Parag V, Waters J

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[Intervention Review]

Pentoxifylline for treating venous leg ulcers

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ABSTRACT

Background

Healing of venous leg ulcers is improved by the use of compression bandaging but some venous ulcers remain unhealed, and some people are unsuitable for compression therapy. Pentoxifylline, a drug which helps blood flow, has been used to treat venous leg ulcers.

Objectives

To assess the effects of pentoxifylline (oxpentifylline or Trental 400) for treating venous leg ulcers, compared with a placebo or other therapies, in the presence or absence of compression therapy.

Search methods

For this fifth update we searched the Cochrane Wounds Group Specialised Register (searched 20 July 2012); The Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2012, Issue 7); Ovid MEDLINE (2010 to July Week 2 2012); Ovid MEDLINE (In-Process & Other Non-Indexed Citations, July 19, 2012); Ovid EMBASE (2010 to 2012 Week 28); and EBSCO CINAHL (2010 to July 13 2012).

Selection criteria

Randomised trials comparing pentoxifylline with placebo or other therapy in the presence or absence of compression, in people with venous leg ulcers.

Data collection and analysis

One review author extracted and summarised details from eligible trials using a coding sheet. One other review author independently verified data extraction.

Main results

No new trials were identified for this update. We included twelve trials involving 864 participants. The quality of trials was variable. Eleven trials compared pentoxifylline with placebo or no treatment. Pentoxifylline is more effective than placebo in terms of complete ulcer healing or significant improvement (RR 1.70, 95% CI 1.30 to 2.24). Pentoxifylline plus compression is more effective than placebo plus compression (RR 1.56, 95% CI 1.14 to 2.13). Pentoxifylline in the absence of compression appears to be more effective than placebo or no treatment (RR 2.25, 95% CI 1.49 to 3.39).

More adverse effects were reported in people receiving pentoxifylline (RR 1.56, 95% CI 1.10 to 2.22). Nearly three-quarters (72%) of the reported adverse effects were gastrointestinal.

Authors' conclusions

Pentoxifylline is an effective adjunct to compression bandaging for treating venous ulcers and may be effective in the absence of compression. The majority of adverse effects were gastrointestinal disturbances.

PLAIN LANGUAGE SUMMARY

Pentoxifylline for treating venous leg ulcers.

Venous leg ulcers are a common, recurring and disabling condition. The mainstay of treatment is the use of firm compression bandages or stockings to support the veins of the leg. Some leg ulcers take many months or years to heal and treatment is aimed at preventing infection and speeding up healing. Pentoxifylline is a tablet taken to improve blood circulation. The review of trials suggests that pentoxifylline, 400 mg tablet taken three times a day, increases the chance of healing.

BACKGROUND

Leg ulcers are wounds on the lower limb that have remained unhealed for four to six weeks. The condition is thought to affect about one per cent of the population at some time in their life, with more women than men being affected (Callam 1985). Point or period prevalence of leg ulcers ranges from 0.4/1000 to 1.9/1000 population and prevalence increases with age (Callam 1985; Baker 1991; Walker 2002a). Approximately 50 to 70% of leg ulcers are venous in origin. Prevalence of venous ulcers ranges from 0.62/1000 to 1.6/1000 (Baker 1991; Nelzén 1994). It is likely that both these estimates are underestimating actual prevalence, as capture-recapture analysis to estimate missing cases in another prevalence study suggested a substantially greater prevalence than these studies identified (Walker 2002b).

The association between calf-pump insufficiency and ulceration has long been known (Browse 1983). Two hypotheses have been advanced to explain the microcirculatory changes observed with venous ulceration. Browse 1982 proposed that venous hypertension increases capillary permeability leading to the formation of an impermeable pericapillary fibrin cuff causing local tissue ischaemia. However, Coleridge Smith 1988 argued that the fibrin cuff is secondary to occlusion of capillaries by plugs of white cells, which creates distal ischaemia. The trapped white cells release agents which damage the endothelium, increasing capillary permeability and allowing the formation of the fibrin cuff. More recently, Coleridge Smith 1993 has suggested that it is the infiltration of the skin by white cell products alone that mediates tissue destruction.

Pentoxifylline, a haemorheological agent, is known to influence microcirculatory blood flow and oxygenation of ischaemic tissues, although the actual mechanism of action is uncertain (Brenner 1987; Stellin 1989). It is thought to increase red and white cell filterability, and decrease whole blood viscosity, platelet aggregation and fibrinogen levels (Brenner 1987; Colgan 1990a).

Another Cochrane review has shown that compression therapy increases the proportion of healed venous ulcers (O'Meara 2012). However, despite the use of compression, a proportion of venous ulcers remain unhealed and therapies additional to compression may be beneficial. Pentoxifylline as an adjunct to compression therapy in venous ulcers has been the subject of trials that have reported conflicting results (Colgan 1990; Dale 1999). Pentoxifylline has also been compared with placebo without compression as standard therapy (Weitgasser 1983).

OBJECTIVES

To assess the effects of pentoxifylline in the treatment of venous leg ulcers, when compared with placebo, both as an adjunct to, and in the absence of compression therapy.
To determine whether pentoxifylline improves the healing of venous leg ulcers when compared with other therapies.

METHODS

Criteria for considering studies for this review

Types of studies

We included trials if the allocation of participants was described as randomised. Trials must have used an objective or operationalised measure of healing.

Types of participants

We included studies involving people of any age in any care setting described as having venous leg ulcers. As there is no agreed standard for the diagnosis of venous ulceration, it was not possible to apply a standard definition. As a minimum, diagnosis of venous disease had to be derived from clinical signs and symptoms consistent with venous hypertension (i.e. ulcer located in the medial gaiter area; presence of varicose veins, eczema, pigmentation, induration and oedema, in any combination).

Types of interventions

1. pentoxifylline compared with placebo (without compression);
2. pentoxifylline compared with placebo (with compression);
3. pentoxifylline compared with other therapy (with or without compression).

Types of outcome measures

Primary outcomes

- time to complete healing;
- numbers of leg ulcers completely healed;
- percentage change in ulcer area.

Secondary outcomes

- adverse effects;
- cost.

Search methods for identification of studies

Electronic searches

The search methods section for the fourth update of this review can be found in Appendix 1.

For this fifth update we searched the following electronic databases:

- The Cochrane Wounds Group Specialised Register (searched 20 July 2012);
- The Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2012, Issue 7);
- Ovid MEDLINE (2010 to July Week 2 2012)
- Ovid MEDLINE (In-Process & Other Non-Indexed Citations, July 19, 2012);
- Ovid EMBASE (2010 to 2012 Week 28);
- EBSCO CINAHL (2010 to July 13 2012)

The following search strategy was used in The Cochrane Central Register of Controlled Trials (CENTRAL):
#1 MeSH descriptor Leg Ulcer explode all trees
#2 (varicose NEXT ulcer*) or (venous NEXT ulcer*) or (leg NEXT ulcer*) or (foot NEXT ulcer*) or (stasis NEXT ulcer*) or ((lower

NEXT extremit*) NEAR/2 ulcer*) or (crural NEXT ulcer*) or "ulcus cruris":ti,ab,kw
#3 (#1 OR #2)
#4 MeSH descriptor Pentoxifylline explode all trees
#5 pentoxifylline or oxpentifylline
#6 trental or torental or techlon or tarontal or sipental or hemovas or harine or felxital or elorgan or ebisan or ceretal or azupentat or artal
#7 (#4 OR #5 OR #6)
#8 (#3 AND #7)

The search strategies for Ovid MEDLINE, Ovid EMBASE and EBSCO CINAHL can be found in Appendix 2, Appendix 3 and Appendix 4 respectively. The Ovid MEDLINE search was combined with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision); Ovid format (Lefebvre 2011). The EMBASE and CINAHL searches were combined with the trial filters developed by the Scottish Intercollegiate Guidelines Network (SIGN) (SIGN 2008). We did not apply any date or language restrictions.

Searching other resources

We searched the bibliographies of all retrieved and relevant publications identified by these strategies for further studies. We contacted the manufacturer (Sanofi-Aventis) through the Australasian office for details of studies on pentoxifylline in leg ulcers, this was not repeated for this update.

Data collection and analysis

Selection of studies

Two review authors (BA, AJ) independently assessed titles and abstracts of studies from the search for relevance and design, in accordance with the selection criteria. We obtained articles if they satisfied the inclusion criteria, or if there was any doubt regarding exclusion. Two review authors (AJ, BA) independently selected the trials for inclusion; we resolved disagreements by discussion.

Data extraction and management

One review author extracted data unblinded (AJ) and another review author checked this for accuracy (JW).

Assessment of risk of bias in included studies

We assessed the risk of bias of each included study using the Cochrane Collaboration tool for assessing risk of bias (Higgins 2009). This tool addresses specific domains, namely sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and other issues (e.g. extreme baseline imbalance)(see Appendix 5 for details of criteria on which the judgement will be based). A risk of bias table was completed for each eligible study.

We will present assessment of risk of bias using a 'risk of bias summary figure', which presents all of the judgments in a cross-tabulation of study by entry. This display of internal validity indicates the weight the reader may give the results of each study (see Figure 1; Figure 2).

Figure 1. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.

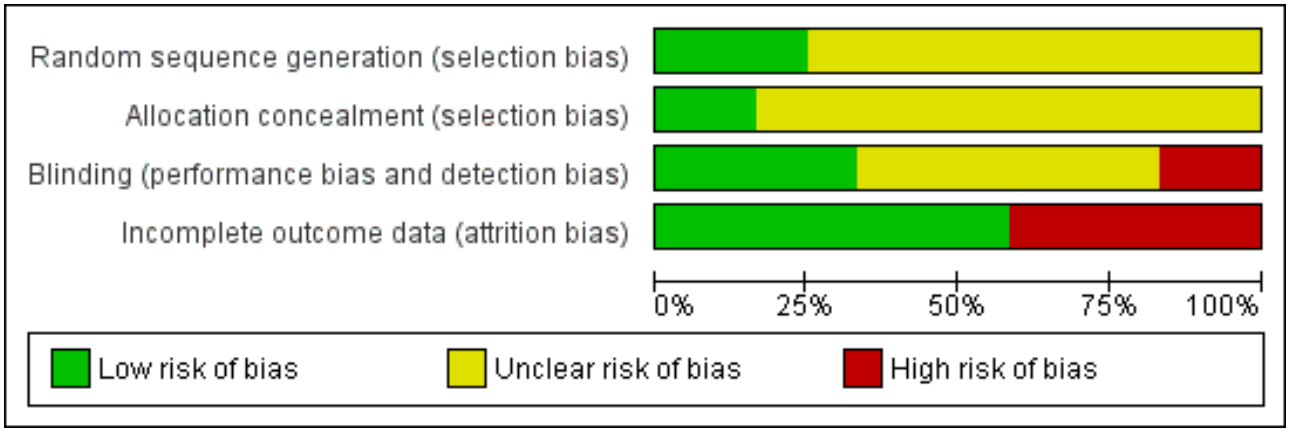


Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

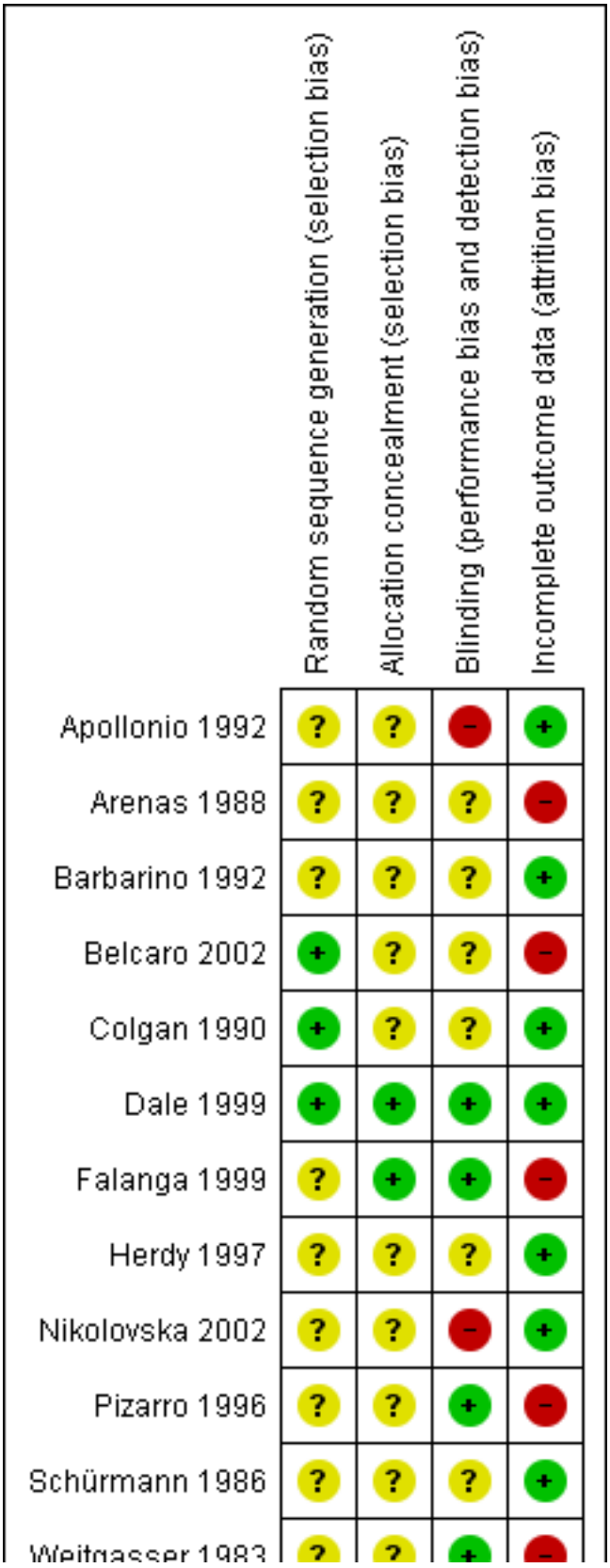
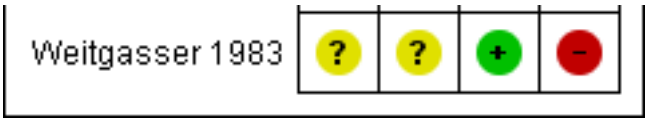


Figure 2. (Continued)



Data synthesis

We expressed results as risk ratio (RR) with 95% confidence intervals (CI). In the absence of significant heterogeneity, we used a fixed effects model when combining studies. Where heterogeneity was significant, we used a random effects model. Where trials excluded withdrawals after randomisation from the analysis, the withdrawals were incorporated back into the study results, either in the group from which they withdrew (if identified) or as failures in the treatment group. We calculated the number needed to treat from the pooled risk ratio using the formula 1/((RR-1) X PEER), where the patient expected event rate (PEER) was the lowest and highest control group event rate from among the pooled trials, as suggested in the Cochrane Reviewers Handbook 4.2.0 (Clarke 2003). Values for the NNT were rounded up to nearest whole number. To examine the extent that publication bias may have influenced findings, we used Begg and Mazumdar's rank correlation test (Begg 1994), a statistical analogue of testing the funnel plot for symmetry by "eye-ball".

Subgroup analysis and investigation of heterogeneity

We specified subgroup analyses prior to synthesis of the studies; these comparisons included pentoxifylline compared with placebo or no treatment, with compression as a background therapy, pentoxifylline compared with placebo or no treatment, and pentoxifylline compared with other drug treatments. We assessed statistical heterogeneity using Chi-square and I^2 (Higgins 2002; Higgins 2003). The I^2 indicates the percentage of between-study variation explained by true heterogeneity rather than chance effect. Where statistical heterogeneity was present ($p<0.1$), the likely cause was investigated using pre-specified sensitivity analyses, to compare the impact of variations in methodology (allocation concealment, blinding, outcome), treatment (duration of treatment, absence of compression) and sample population. Probable cause was indicated when I^2 returned to near zero levels.

RESULTS

Description of studies

Results of the search

In the searches for this review, we assessed 69 citations (de duplicated across multiple databases). We included 12 trials and excluded 14 from the review. We did not identify any unpublished studies. We obtained further information to clarify details of the reports from trialists involved in Schürmann 1986; Colgan 1990; Dale 1999 and Falanga 1999.

Included studies

Twelve trials met the inclusion criteria; 11 trials compared pentoxifylline with placebo (Weitgasser 1983; Schürmann 1986; Arenas 1988; Colgan 1990; Barbarino 1992; Pizarro 1996; Herdy 1997; Dale 1999; Falanga 1999; Belcaro 2002) or no treatment (Nikolovska 2002) and one trial compared pentoxifylline with the anticoagulant defibrotide (Apollonio 1992).

Compression was a standard treatment in seven studies (Schürmann 1986; Apollonio 1992; Barbarino 1992; Pizarro 1996; Dale 1999; Falanga 1999; Belcaro 2002). The type of compression varied between studies and within one study: two layer systems were used by Colgan 1990; Apollonio 1992; Barbarino 1992 and Belcaro 2002; Unna boot was used by Falanga 1999; and Dale 1999 used both single layer and four layer systems balanced within a factorial trial. Schürmann 1986 also used short stretch bandages (personal communication, R Eberhardt), while Pizarro 1996 did not describe the type of bandages used. Four studies compared pentoxifylline with matching placebo (Weitgasser 1983; Arenas 1988; Herdy 1997) or no systemic treatment (Nikolovska 2002), in the absence of compression.

The trials varied in the method used to diagnose venous ulceration. Nine trials reported the method of diagnosis: Arenas 1988 used clinical history and the presence of palpable pulses; Colgan 1990 used clinical examination and ankle brachial pressure index (ABPI) >0.8; Barbarino 1992 used ABPI>0.8, venous ankle pressure (Bartolo's method), valvular incompetence and presence of venous reflux as determined by continuous wave Doppler ultrasound; Pizarro 1996 determined the presence of venous insufficiency using photoplethysmograph, pneumoplethysmography, Doppler venous studies and ABPI; Herdy 1997 used clinical assessment without specifying what this meant; Dale 1999 used clinical assessment, ABPI>0.8 and presence of venous reflux as determined by continuous wave Doppler ultrasound (Prescott 1998); Falanga 1999 used clinical assessment (presence of hyperpigmentation, lipodermatosclerosis, varicose veins and medial location of ulcer) and presence of venous reflux as determined by continuous wave Doppler ultrasound; Belcaro 2002 used clinical examination, ABPI 0.8 to 1.1, and colour duplex scanning; Nikolovska 2002 used clinical signs (hyperpigmentation, lipodermatosclerosis, varicosities and oedema), ABPI>0.85 and venous refilling time < 25 seconds as determined by photoplethysmograph.

The majority of trials attempted to include only participants with venous aetiology by excluding participants with other diseases likely to cause ulceration (Arenas 1988; Apollonio 1992; Barbarino 1992; Herdy 1997; Dale 1999; Falanga 1999; Belcaro 2002; Nikolovska 2002). One trial implied that people with concurrent diseases such as diabetes were included (Weitgasser 1983). Colgan 1990 included people with diabetes if their ulcer was considered venous in origin. All the people with diabetes in this trial were in the pentoxifylline arm (Colgan 1990b).

Five of the 12 studies did not report the setting in which the trial took place (Weitgasser 1983; Schürmann 1986; Arenas 1988; Apollonio 1992; Herdy 1997); five of the remaining studies were community based (Colgan 1990; Pizarro 1996; Dale 1999; Falanga 1999; Belcaro 2002). Barbarino 1992 admitted all people to hospital

for seven days, and then discharged them to community treatment. Nikolovska 2002 recruited both inpatients and outpatients.

The duration of ulceration prior to inclusion in the trial was specified in five of the 12 trials (Colgan 1990; Barbarino 1992; Dale 1999; Falanga 1999; Belcaro 2002); the mean or median ulcer duration prior to trial entry was four to 26 months. Two studies did not report the required duration prior to trial entry, but specified therapy-resistant ulcers as an inclusion criteria (Weitgasser 1983; Apollonio 1992).

It is assumed that all trials used oral medication. The oral dose was 1200 mg daily (in three divided doses) in all studies, with the exception of Falanga 1999 who also compared 2400 mg daily (in three divided doses) in a three arm trial. Barbarino 1992 also included an intravenous dose (400 mg daily in two divided doses), in addition to the oral dose, for the duration of the seven day hospital stay.

Excluded studies

In previous searches 14 out of the 30 studies retrieved clearly did not meet the inclusion criteria: one because the outcome was a physiological assay not meaningful to patients (Mirshahi 1995); one because group allocation was not randomised (Angelides 1992), and 12 because they were uncontrolled trials (Krstic 1979; Pemler 1979; Weitgasser 1982; Dvorkin 1985; Herger 1986; Galbiati 1987; Angelides 1989; Palomares 1991; de Freitas 1995; Koshkin 1996; Trattner 1996; Chodynicka 1999). In addition, we have now excluded two trials that were previously awaiting assessment as the authors had been approached for more detail: one trial because the corresponding author is unwilling to contribute the study to a meta-analysis, a statistical procedure he considers misleading (de Sanctis 2002), and the second trial reported as a conference abstract because there has been no response to correspondence sent to the author and electronic searching has failed to reveal an email address or the full text publication of the study (Marchitelli 1992), both of these trials were positive trials with more healing in the pentoxifylline groups than the comparison groups..

Risk of bias in included studies

Studies varied in risk of bias and/or reporting of methods. All studies were described as randomised controlled trials, randomisation strategies being reported in only two studies (Colgan 1990; Dale 1999), although one trial (Belcaro 2002) stated they followed the same method as Colgan 1990. Allocation concealment was reported in two trials (Dale 1999; Falanga 1999). Eight studies were described as double-blind comparisons of pentoxifylline with a placebo (Weitgasser 1983; Arenas 1988; Colgan 1990; Barbarino 1992; Pizarro 1996, Dale 1999; Falanga 1999; Belcaro 2002), although only four studies described how a level of blinding was achieved (Weitgasser 1983; Pizarro 1996; Dale 1999; Falanga 1999). One trial was described as a single-blind comparison, but did not describe who was blinded (Schürmann 1986). None of the eight blinded trials reported any un blinding of patients, so it was assumed that blinding was satisfactory. One trial did not report blinding (Herdy 1997) and two trials were not blinded (Apollonio 1992; Nikolovska 2002).

With the exception of two trials (Weitgasser 1983; Arenas 1988) all studies reported objective data from which comparisons could be established. We included Weitgasser 1983 and Arenas 1988 because they had operationally defined an outcome (i.e. complete healing, significant improvement) and were reported as double blind; therefore a subjectivity in the assessment of significant improvement would apply across both groups. Three trials (Dale 1999; Falanga 1999; Nikolovska 2002) reported a priori sample size calculations. One trial (Dale 1999) reported use of an intention to treat analysis. Falanga 1999 used intention to treat analysis for all people who had enrolled and for whom one follow-up visit was documented but this trial excluded two participants from their final analysis. Six other studies either had no withdrawals (Schürmann 1986; Apollonio 1992; Barbarino 1992; Herdy 1997) or included the withdrawals in the analysis as treatment failures (Colgan 1990; Nikolovska 2002). The remaining studies excluded withdrawals from their analysis.

Two trials did not report any data on baseline comparability (Schürmann 1986; Apollonio 1992), although Schürmann stated data was comparable and baseline mean ulcer size was able to be calculated from outcome data (ulcer size at baseline and conclusion for each patient).

Table 1 summarises criteria by trial and risk of bias summary figures: Figure 1; Figure 2

Effects of interventions

The majority of studies reported either complete healing of the reference ulcer or all ulcers on the reference leg as the primary outcome, or provided individual data from which proportions healed could be calculated. In one study (Falanga 1999) proportions healed were extrapolated from the life table analysis. Herdy 1997 reported the area for each participant's ulcer at baseline and trial completion. No ulcers completely healed. Rather than report a single trial as continuous data, the operational definitions for healing or significant improvement from Arenas 1988 were applied to create categorical data from Herdy 1997. No ulcers met this criterion in either arm. One trial (Falanga 1999) compared two different doses of pentoxifylline (1200 mg and 2400 mg daily) with the placebo. For the purposes of this analysis, the two treatment arms were added together and we conducted sensitivity analyses to test the impact of this. In addition, this study also excluded 2 participants after randomisation. These participants have been added to the denominator in the treatment arm as treatment failures, in order to prevent over-estimation of the treatment effect. Another trial (Pizarro 1996) was a four arm trial, in which two arms received the same dose of pentoxifylline and two arms received a placebo. Following advice from the Cochrane Wound Groups editorial base, we decided to combine the two pentoxifylline arms and the two placebo arms.

Pentoxifylline compared with placebo or no treatment

Complete Healing or Significant Improvement

Eleven trials (Weitgasser 1983; Schürmann 1986; Arenas 1988; Colgan 1990; Barbarino 1992; Pizarro 1996; Herdy 1997; Dale 1999; Falanga 1999; Belcaro 2002; Nikolovska 2002) involving 841 participants were combined using a random effects model. Participants receiving pentoxifylline were more likely to heal than those receiving the control treatment (RR 1.70, 95% CI 1.30 to 2.24) (Analysis 1.1). However, the test for heterogeneity was significant and 60% of the between study variation was due to heterogeneity rather than chance. We conducted sensitivity analyses to test the relative impacts of blinding (excluding single or open label trials)(Analysis 1.2), treatment duration (excluding trials with short

treatment regimens)(Analysis 1.3), outcome choice (excluding trials reporting complete healing and significant improvement)(Analysis 1.4), treatment choice (excluding trials not using compression) (Analysis 1.5) and type of participant (excluding trials that recruited hard-to-heal participants)(Analysis 1.6). The I^2 respectively was 65.4%, 69.8%, 62.5%, 64.3% and 0.3%. Heterogeneity was near-zero when trials that specifically recruited hard-to-heal participants were excluded. We were not able to test the impact of allocation concealment, as only one trial had reported explicitly how allocation was concealed up to the point of randomisation.

Side Effects

Nine trials (Weitgasser 1983; Schürmann 1986; Arenas 1988; Colgan 1990; Barbarino 1992; Herdy 1997; Dale 1999; Falanga 1999; Nikolovska 2002) involving 549 participants were combined using a fixed effects model. The incidence of side effects was significantly higher in people treated with pentoxifylline (RR 1.56, 95% CI 1.10 to 2.22)(Analysis 1.7), although this result was sensitive to the exclusion of Nikolovska 2002, an open label study (RR 1.28, 95%CI 0.89 to 1.84). In studies that described adverse effects, the majority of side effects in pentoxifylline treated participants were gastrointestinal disturbances (72%). Three trials (Schürmann 1986; Barbarino 1992; Herdy 1997) that reported side effects had no withdrawals and four trials (Arenas 1988; Colgan 1990; Dale 1999; Nikolovska 2002) that reported side effects also reported reasons for withdrawals; 30% of participants reporting side-effects in the seven trials cited side effects as the reason for withdrawal.

Begg's adjusted rank correlation test for the 11 trials in which pentoxifylline was compared to either placebo or no treatment (excluding the trial that had zero events in both groups) indicated publication bias to be unlikely (Spearman correlation coefficient r=0.079, p=0.83).

Pentoxifylline with compression

Seven trials (Schürmann 1986; Colgan 1990; Barbarino 1992; Pizarro 1996; Dale 1999; Falanga 1999; Belcaro 2002) involving 659 participants were combined using a random effects model. Participants receiving pentoxifylline were more likely to heal than those receiving compression plus placebo (RR 1.56, 95% CI 1.14 to 2.13)(Analysis 2.1). However, the test for heterogeneity was significant and 64% of the between-study variation was due to heterogeneity rather than chance. Three trials (Colgan 1990; Barbarino 1992; Belcaro 2002) recruited hard-to-heal participants. When these trials (n=264) were combined using a fixed effects model, participants receiving pentoxifylline were more likely to heal than those receiving compression plus placebo (RR 2.36, 95% CI 1.74 to 3.19)(Analysis 2.2). This result was robust to combination using a random effects model. Participants receiving pentoxifylline in trials that did not specifically recruit hard-to-heal participants were also more likely to heal than those receiving placebo although with reduced effect (RR 1.20, 95% CI 1.01 to 1.43)(Analysis 2.3).

Pentoxifylline without compression

Four trials (Weitgasser 1983; Arenas 1988; Herdy 1997; Nikolovska 2002) involving 182 participants were combined using a fixed effects model. Participants receiving pentoxifylline were more likely to heal than those receiving the control treatment (RR 2.25, 95% CI 1.49 to 3.39)(Analysis 3.1). This result was robust to combination using a random effects model. As there was very little heterogeneity, and only one trial recruited participants with hard-to-heal ulcers, no sensitivity analysis was performed.

Pentoxifylline compared with defibrotide (compression as standard therapy)

One trial (Apollonio 1992) involving 23 participants compared defibrotide with pentoxifylline (all patients received compression as a standard therapy). There was no significant difference in healing at three months (RR 1.12, 95% CI 0.81 to 1.55)(Analysis 4.1). All trial participants had healed ulcers by six months.

DISCUSSION

On the basis of current evidence pentoxifylline appears to be an effective treatment for venous leg ulcers, either as an adjuvant to compression, or alone where compression cannot be used. Most side effects were gastrointestinal effects, and were tolerated by participants.

Pentoxifylline with compression

Pentoxifylline is an effective adjunct to compression therapy. Overall there was an absolute increase in healing of 21% (95%CI 8 to 34%) in favour of pentoxifylline as an adjuvant to compression. As control event rates ranged from a high of 62.2% to a low of 16.67%, the NNT may range from 3 (95%CI 2 to 12) to 11 (95%CI 6 to 43). The cost-effectiveness of pentoxifylline and compression was reported alongside one of the included trials (Bosanquet 1995; Dale 1999), but this information has yet to be fully reported. However, economic modelling involving four of the trials that used pentoxifylline as an adjuvant to compression (Schürmann 1986; Colgan 1990; Dale 1999; Falanga 1999) suggested a mean cost saving of GBP 98.09 (95%CI -49.21 to 245.00) per QALY gained if pentoxifylline was used (Iglesias 2006). The dominance of pentoxifylline if the other three trials were included in an economic analysis is currently unknown. However, it seems most likely that pentoxifylline would remain the dominant economic strategy given the additional trials favoured pentoxifylline.

Where participants were sampled from a hard-to-heal population, the absolute increase in healing was 37% (95% CI 26 to 48%). As control event rates ranged from a high of 28.6% to a low of 16.67%, the NNT may range from 7 (95%CI 4 to 25) to 11 (95%CI 6 to 43). Other trials may also have inadvertently recruited hard-to-heal participants as part of their sample. An individual patient data meta-analysis using a prognostic index could test the hypothesis that pentoxifylline is more effective as an adjuvant in hard-to-heal populations and "normal healing" participants.

Pentoxifylline without compression

Pentoxifylline appears to be more effective than placebo or no treatment in the absence of compression. The absolute increase in healing was 23% (95%CI 4 to 43). As control event rates ranged from a high of 27.5%% to a low of 23.3%, the NNT may range from 3 (95%CI 2 to 8) to 4 (95%CI 2 to 9). This finding suggests it should be considered for use in people unable to tolerate compression bandaging, or those who do not want to use compression.

Limitations

Subgroup analyses are observational and thus prone to bias. In addition subgroup using a threshold of 5% for statistical significance means there is a 1:20 chance that a subgroup

analysis will be significant by chance alone. Although hard-to-heal participant populations appear to explain the statistical heterogeneity amongst the included trials, such a conclusion may be misleading. Therefore these analyses should be considered exploratory rather than conclusive.

Although analysis suggests publication bias is unlikely to be present, the threat cannot be ruled out. We have received advice that a negative study of pentoxifylline in venous ulceration remains unpublished (possibly called the PRIDE study). However, we have not been able to locate any information about such a study, despite [1] the manufacturer searching their internal database, [2] requests for more information from the two sources of the information, and [3] letters to relevant journals. If any readers have information about such a negative trial, we would welcome their contacting us. In the absence of such information, we calculated a fail-safe N (Rosenthal 1984) to determine how many unpublished null studies would be necessary to reduce our findings from significant to non-significant: 120 null studies would be needed. It should be noted that the fail-safe N can only be an overestimate of the number of negative studies needed to refute our findings (Soeken 2003). However, until credible information becomes available about a negative study, we believe current evidence supports the use of pentoxifylline.

AUTHORS' CONCLUSIONS

Implications for practice

Pentoxifylline is an effective adjunct to compression bandaging for treating venous ulcers. In the absence of compression, pentoxifylline also appears to be effective for treating venous ulcers. The majority of adverse effects were gastrointestinal disturbances (nausea, indigestion and diarrhoea).

Implications for research

The quality of the research and reporting was variable, with early studies being of poorer quality. Important messages for future studies are:

1. Future trials should be registered with a WHO approved registry.
2. The CONSORT statement (Moher 2001) should be used as a guideline for reporting.
3. Recruitment numbers should be based on an a priori sample size calculation given that the likely treatment benefit can now be inferred.
4. Compression therapy should be clearly described, to assist with appropriate combination of trials.
5. Objective outcome measures should be used. Examples include complete healing or absolute change in ulcerated area (including standard deviations). Time to healing, whether average or median, is an important outcome for clinical practice, but is infrequently reported.
6. Where multiple ulcers exist, complete healing of all ulcers, even if bilateral, should be the endpoint in a drug trial.
7. Short duration trials should be avoided.
8. Analysis should be by intention-to-treat of all people following randomisation.
9. An economic analysis incorporating recently located trials should be undertaken.

Areas for further investigation include:

1. An individual participant meta-analysis to test the relative effects of pentoxifylline on participants meeting criteria for slow-to-heal ulcers in comparison with those that might be considered "normal" healers.
2. Cost effectiveness in people unable to tolerate compression.
3. Trials of lower doses to test efficacy and tolerability.
4. Trials to test effect on prevention of recurrence.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Apollonio 1992

Methods	RCT; two arm parallel group; blinding not reported; two treatments.
Participants	23 participants; setting not stated. Inclusion criteria: venous ulcers unresponsive to local therapy. Exclusion criteria: ulcers of arterial, lymphatic, dermatological, infectious, neoplastic, neurotrophic or mixed vascular origin. Mean age: Gp1. 46 years, Gp2. 51 years. Mean ulcer size: Gp1. 19.6 cm^2, Gp2. 18.1 cm^2. Mean venous pressure: Gp1. 109 mmHg, Gp2. 112 mmHg. Obesity: Gp1. 5, Gp2. 4. Mean duration of ulcer (overall): 5.3 months.
Interventions	Group 1: (n=12) defibrotide 800mg in two divided doses daily. Group 2: (n=11) pentoxifylline 400mg tds. Treatment duration: 6 months.
Outcomes	Complete healing at 3 months: Gp1. 11/12 (92%), Gp2. 9/11 (82%). Complete healing at 6 months: Gp1.12/12, Gp2. 11/11. Mean reduction in size at 3 months (cm^2): Gp1. 18.32 , Gp2. 14.94. Side effects: Gp1. 1/12, Gp2. 4/12. Withdrawals: nil.
Notes	A third selected cohort receiving no treatment was used as a comparison group.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "This randomized study ...". Comment: No reason to doubt this statement but method for achieving randomisation not reported. The baseline table is broadly equivalent, although with some differences between groups, but to be expected with small numbers.
Allocation concealment (selection bias)	Unclear risk	Comment: No description of allocation concealment or blinding (which would generally facilitate allocation concealment if blinding is organised through third party).
Blinding (performance bias and detection bias) All outcomes	High risk	Comment: No description in abstract or translation of methods and materials and presumed not to have been done, given active treatments.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: 23 patients enrolled in two active arms and 23 patients followed up.

Arenas 1988

Methods	RCT; two arm parallel group; double blind; matching placebo.
Participants	30 participants; setting not stated. Inclusion criteria not reported.

Arenas 1988 *(Continued)*

	Exclusion criteria: Buerger's disease; vascular surgery within previous 3 months; history of lumbar sympathectomy; acute thrombotic disease; hypersensitivity to xanthines; addiction to analgesia; anticoagulant/vasoactive or antiplatelet medication within previous 4 weeks; metabolic or haemorrhagic disorders; severe infection. No data reported on baseline comparability.
Interventions	Group 1: (n=18) pentoxifylline 400mg tds. Group 2: (n=12) placebo. Treatment duration: six months.
Outcomes	Healing & significant improvement (operationalised as complete closure or > 60% reduction in size): Gp1. 7/18 (39%), Gp2. 3/12 (25%). Side effects: Gp1. 3/18, Gp2. 0/12. Withdrawals: (n=5) Gp1. 3, Gp2. 2. Reasons: inadequately reported.
Notes	Data not clearly reported; total numbers involved the trial may be 32, not 30. Number of participants greater in pentoxifylline group, raising questions about randomisation.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "A randomized double-blind comparison between pentoxifylline and placebo was conducted in 30 patients". Comment: No reason to doubt random generation, but method for achieving randomisation not reported and baseline table not presented.
Allocation concealment (selection bias)	Unclear risk	Quote: "A randomized double-blind comparison between pentoxifylline and placebo was conducted in 30 patients". Comment: Unclear as method for achieving blinding (which would generally facilitate allocation concealment if blinding organised through third party) not reported.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "A randomized double-blind comparison between pentoxifylline and placebo was conducted in 30 patients". Comment: Method for blinding not reported, although described as double-blind. Probably done but cannot be completely assured.
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "Treatment was discontinued in five patients [30 randomised] ... Evaluation performed on 15 patients from the pentoxifylline group and 10 patients from the placebo group". Comment: Five patients excluded from analysis.

Barbarino 1992

Methods	RCT; two arm parallel group; double blind; matching placebo
Participants	12 participants treated for one week as inpatient and eight weeks as outpatients. Inclusion criteria: ulcer>two years duration, ulcer resistant to conventional therapy, ABI > 0.8. Exclusion criteria: chronic peripheral obstructive arterial disease; diabetes; disorders of circulatory system. Mean age: Gp1. 63 years, Gp2. 65 years. Mean ulcer duration: Gp1. 27 months, Gp2. 26 months. Mean ulcer size: Gp1. 14.1 cm^2, Gp2. 14.5 cm^2. Mean ABI: Gp1. 0.84, Gp2. 0.85.
Interventions	Group 1: (n=6) pentoxifylline 400mg tds, plus two layer compression bandaging.

Barbarino 1992 *(Continued)*

	Group 2: (n=6) placebo plus two layer compression bandaging. Treatment duration: seven days inpatient, 60 days outpatient.
Outcomes	Complete healing: Gp1. 4/6 (66%), Gp2. 1/6 (17%). Mean reduction in ulcer size (percent): Gp1. 91%, Gp2. 58%. Side effects: Gp1. 2/6 (33%), Gp2. 1/6 (17%). Nil withdrawals.
Notes	Each participant tested for responsiveness to treatment prior to randomisation and then underwent washout period for two weeks. During hospitalisation, participants received 200mg intravenous pentoxifylline twice daily in addition to oral dose (1200mg) or matching placebo.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Six patients were allocated at random to receive ... The control group received matching placebo in an identical regimen". Comment: No reason to doubt random generation as baseline table equivalent, but method for achieving randomisation not reported.
Allocation concealment (selection bias)	Unclear risk	Comment: Unclear as method for achieving blinding (which would generally facilitate allocation concealment if blinding organised through third party) not reported.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "The control group received matching placebo in an identical regimen." Comment: Method for blinding not reported, although described as double-blind. Probably done but cannot be completely assured.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: Individual case data presented for each participant at baseline and end of study. Complete case follow up achieved.

Belcaro 2002

Methods	RCT; two arm parallel group; method reported to follow that of Colgan 1990; double blind; matching placebo.
Participants	172 participants; outpatient clinics. Inclusion criteria: Ulcers unhealed after two months outpatient treatment; ulcer size 2-15cm2; ABI>0.8, clinically venous and colour duplex scanning indicated ulcer due to venous hypertensive microangiopathy. Exclusion criteria: ABI>1.1; any vascular disease; diabetics; any other disease requiring pharmacological treatment. Mean age: Gp1. 64 years, Gp2. 64 years. Mean ulcer duration: Gp1. 4 months, Gp2. 4 months. Mean ulcer size: Gp1. 5.3cm2, Gp2. 5.0cm2. Mean ABI: not reported.
Interventions	Group 1 (n=84): pentoxifylline 400mg tds plus two layer compression bandaging (Dauerbinde). Group 2 (n=88): placebo plus two layer compression bandaging. Treatment duration: Until healed or six months.
Outcomes	Complete healing: Gp1. 55/84 (65%), Gp2. 24/88 (27%). Mean reduction in ulcer size: Gp1. 87%, Gp2. 47%. Side effects: Authors state no important side effects observed.

Belcaro 2002 *(Continued)*

	Withdrawals: (n=12), Gp1. 2/84 (2%), Gp2. 10/88 (11%). Reasons: Unclear.
Notes	Complete healing = complete epithelialisation of reference ulcer (largest ulcer on leg). Treatment with PTX increased management costs by 21%; non-healing in group two increased management costs by 44%. Difference significant (p<0.05).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "This independent study (prospective, randomized, double-blind and placebo-controlled) was conducted in GCP according to the protocol published by Colgan and associates ...". Comment: No reason to doubt random generation as baseline table equivalent, but method for achieving randomisation not reported in this study report however the study by Colgan did undertake adequate sequence generation.
Allocation concealment (selection bias)	Unclear risk	Comment: Unclear as method for achieving blinding (which would generally facilitate allocation concealment if blinding organised through third party) not reported.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "This independent study (prospective, randomized, double-blind and placebo-controlled) ... ". Comment: Probably done, although method not described.
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "One hundred seventy-two patients were included and 160 completed the study (82 equivalent to 97.6% in the PXF group and 78 out of 88 equivalent to 88.6% in the placebo group) ... Complete healing of the reference ulcer occurred in 55 of 82 (67%) in the PXF group and 24 of 78 (30.7%) ...". Comment: 12 patients excluded from primary analysis, although included in life-table methods, presumably as treatment failures.

Colgan 1990

Methods	RCT; two arm parallel group; double blind; matching placebo
Participants	80 participants in four centres; outpatient clinics. Inclusion criteria: at least two months standard treatment with no improvement, ABI > 0.8, ulcer clinically venous, no contraindication to pentoxifylline. Exclusion criteria: not reported. Mean age (years): Gp1. 71, Gp2. 70. Mean duration of ulcer: Gp1. 6 months, Gp2. 9 months. Mean ulcer size: Gp1. 5.2 cm^2, Gp2. 4.7 cm^2. Mean ABI: Gp1. 1.05, Gp2. 1.06.
Interventions	Group 1: (n=38) PTX 400mg tds, plus two layer compression bandaging. Group 2: (n=42) placebo, plus two layer compression bandaging. Treatment duration: until reference ulcer healed or 24 weeks.
Outcomes	Number healed at 24 weeks: Gp1. 23/38 (60%), Gp2. 12/42 (29%). Side effects: Gp1. 17/38, Gp2. 14/42. Withdrawals: (n=12), Gp1. 3/38, Gp2. 9/42. Reasons: Group 1 - oedema & depression, dyspepsia & diarrhoea, vomiting. Group 2 - purpura, skin rash, dizziness & diarrhoea, cellulitis & pain, headache & nausea, misdiagnosed pemphigoid, poor compliance.

Colgan 1990 *(Continued)*

Notes	Complete healing = complete re-epithelialisation of reference ulcer (largest ulcer) on leg. Block randomisation by separate lists for each centre; allocation concealment not reported. Administrative support provided by drug's manufacturer.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomisation was performed in balanced blocks of eight with a separate list for each centre ... Eighty patients were randomly allocated to receive either oxpentifylline or placebo.".
Allocation concealment (selection bias)	Unclear risk	Quote: Randomisation was performed in balanced blocks of eight with a separate list for each centre". Comment: Probably done, but not clearly stated how allocation concealment achieved, especially as method for achieving blinding (which would generally facilitate allocation concealment if blinding organised through third party) not reported.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "The trial design was a prospective, randomised, double blind, placebo-controlled, parallel group study ... ". Comment: Probably done, although method not described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "The results were analysed by life-table method, which gives the proportion of ulcers healed at each visit and takes into account dropout rates". Comment: Dropouts treated as treatment failures and included in analysis. ITT analysis achieved in essence.

Dale 1999

Methods	Factorial RCT; sequential sealed envelope; double blind; matching placebo
Participants	200 participants in two centres; outpatient centres. Inclusion criteria: Age > 18; duration > two months; ulcer size > 1cm diameter; pure venous aetiology. Exclusion criteria: MI in past three months; haemorrhage in past eight weeks; hypersensitivity to xanthines, pentoxifylline, and drinks containing cola or caffeine; systemic treatment with corticosteroids, cytotoxics, naftidrofuryl, oxyrutin, anticoagulants, fibrinolytics or experimental drugs with last three months; lumbar sympathectomy within last three weeks; presence of right heart failure; serum creatinine > 180 micromol/litre; hepatic insufficiency; diabetes; malignant disease; rheumatoid arthritis or severe connective disorder; limited physical capacity or immobility; infected or gangrenous ulcer; ulcer less than 1cm in one dimension; presence of ulcer < two months; admission to hospital likely to be required for > 10 days; pregnancy, lactation, inadequate contraception; life expectancy < six months. Mean age: Gp1. 71 years, Gp2. 68 years. Median ulcer duration: Gp1. 6 months, Gp2. 4 months. Median maximum ulcer diameter: Gp1. 2.7 cm, Gp2. 2.9 cm.
Interventions	Factorial trial with multiple interventions balanced between groups i.e. two types of compression and two types of dressings evenly balanced between treatment and control groups. Group 1 (n=101): PTX 400mg tds, plus compression (either elastic single layer or four layer bandage), plus wound dressing (knitted viscose or hydrocolloid). Group 2 (n=99): placebo plus compression (either elastic single layer or four layer bandage), plus wound dressing (knitted viscose or hydrocolloid). Treatment duration: 24 weeks
Outcomes	Number healed at 24 weeks: Gp1. 65/101 (64%), Gp2. 52/99 (52%). Side effects: Gp1. 3/101, Gp2. 3/99. Withdrawals: (n=22), Gp1. 11/101, Gp2. 11/99.

Dale 1999 *(Continued)*

	Reasons: side effects (Gp1. 4/101, Gp2. 3/99), no reason (Gp1. 1/101, Gp2. 0/99), medication stopped when patient hospitalised (Gp1. 1/101, Gp2. 3/99), exclusion criteria discovered after entry (Gp1. 2/101, Gp2. 2/99), medication omitted by patient >14 days (Gp1. 1/101, Gp2. 2/99), died (Gp1. 2/101, Gp2. 0/99), intercurrent illness (Gp1. 1/101, Gp2. 0/99).
Notes	Complete healing = healing of all ulcers on reference leg. Intention to treat analysis. A priori sample size calculation. Study supported drug's manufacturer and manufacturer of one compression system (ConvaTec).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomised in a 1:1 ratio, by centre, to receive pentoxifylline in 400 mg three times daily or matching placebo, and they were also randomised to receive one of the two bandaging treatments and one of two dressings ...". Comment: Likely to be adequate sequence generation.
Allocation concealment (selection bias)	Low risk	Quote: "The [drug] treatments were packaged, supplied, and labelled with consecutive patient numbers in each centre by the manufacturer ... The dressings and bandages were allocated by opening the correspondingly numbered, sealed, opaque envelope". Comment: Achieved.
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "The pentoxifylline and placebo tablets looked identical to ensure that the study was double blind with respect to drug". Comment: Achieved.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Twenty two patients were withdrawn from the trial, 11 in each group, but they were included in the analysis as failure to heal on treatment". Comment: Achieved.

Falanga 1999

Methods	RCT; three arm parallel group; double blind; matching placebo.
Participants	129 participants in 14 centres; outpatient clinics. Inclusion criteria: one or more venous ulcers (>1cm in diameter); venous disease; presence of reflux; age 18-90; ulcer duration 2 to 24 months; absence of significant arterial insufficiency (ABI > 0.5); ambulatory; BMI 90 to 150% of ideal; able to give informed consent. Exclusion criteria: pregnancy; allergy to xanthines; lumbar sympathectomy within last 3 months; HbA1c > 10%, presence of diabetic or ischaemic ulcers; ulcers with exposed tendon or bone, infected ulcers needing systemic antibiotics, history of poor compliance with treatment. Mean Age: Gp1. 60 years, Gp2. 58 years, Gp3. 56 years. Mean duration of ulcer (months) : Gp1. 6, Gp2. 6, Gp3. 6. Mean ulcer size: Gp1. 9.6 cm^2, Gp2. 11.4 cm^2, Gp3. 7.7 cm^2. Mean ABI: Gp1. 1.1, Gp2. 1.1, Gp3. 1.1.
Interventions	Group 1: (n=45) placebo plus compression (Unna's boot & elastic bandage). Group 2: (n=41) PTX 400mg tds plus compression. Group 3: (n=43) PTX 800mg tds plus compression. Treatment duration: 24 weeks.
Outcomes	Median time to healing: Gp1. 100 days, Gp2. 83 days, Gp3. 71 days. Number healed at 24 weeks (extrapolated from life-analysis): Gp1. 28/45 (63%), Gp2. 31/41 (75%), Gp3. 31/43 (73%).

Falanga 1999 *(Continued)*

	Side effects: Gp1. 13/45, Gp2. 9/41, Gp3. 15/43. Withdrawals: (n=32) Gp1. 10/45, Gp2. 11/41, Gp3. 11/43. Reasons: not reported.
Notes	Complete healing = healing of all ulcers on reference leg. Intention to treat analysis on all participants who enrolled, received treatment and attended at least one follow-up visit; 129/131 enrolled. Study sponsored by drug's manufacturer.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The study was a multicenter randomized double blind placebo controlled parallel group clinical trial". Comment: Probably done, although method of sequence generation not described.
Allocation concealment (selection bias)	Low risk	Quote: "The 800mg dose of pentoxifylline was given as two tablets of 400 mg each, and the total number of tablets (placebo or pentoxifylline) was the same for all patients. The study drug, pentoxifylline, and the matching placebo tablets, were provided by Hoechst Marion Roussel". Comment: likely allocation was concealed as tablets were provided by Company.
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "The 800mg dose of pentoxifylline was given as two tablets of 400 mg each, and the total number of tablets (placebo or pentoxifylline) was the same for all patients. The study drug, pentoxifylline, and the matching placebo tablets ...". Comment: Achieved.
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "The study enrolled 131 patients at 14 centers, of whom 129 received study treatment and were followed up on at least one occasion (intention to treat population)". Comment: Two patients were randomised but excluded from analysis.

Herdy 1997

Methods	RCT; two arm parallel group; blinding not reported; matching placebo.
Participants	12 participants; setting not reported. Inclusion criteria: venous ulceration. Exclusion criteria: arterial insufficiency. Mean age: Gp1. 58 years, Gp2. 56 years. Mean duration of ulcer: Gp1. 48 months, Gp2. 54 months. Mean ulcer size: Gp1. 9.6 cm^2, Gp2. 6.0 cm^2. No other baseline data reported.
Interventions	Group 1: (n=6) PTX 400mg tds. Group 2: (n=6) placebo. Treatment duration: 12 weeks.
Outcomes	Reduction in ulcer area (cm^2): Gp1. 2.2 cm^2, Gp2. 0.4 cm^2. Side effects: Gp1. 2/6, Gp2. 0/6. Withdrawals: nil.
Notes	Mean size ulcer favoured control at baseline.

Risk of bias

Herdy 1997 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "A isso seguiu-se distribuicao aleatoria dos pacientes selecionados pelos gru-pos de testagem (seis pacientes tratados com pentoxifilina e cuidados gerais) e controle (seis pacientes aos quais se administrou placebo de amido, alem does cuidados gerais) ... [translation - After that, a random distribution of the patients selected was done into the testing (six patients treated with pentoxifylline and general care) and control groups (six patients treated with starch placebo in addition to general care)". Comment: Unclear whether mention of "random distribution" related to random selection of patients or random allocation of patients.
Allocation concealment (selection bias)	Unclear risk	Comment: Unclear as method for achieving blinding (which would generally facilitate allocation concealment if blinding organised through third party) not reported.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "e controle (seis pacientes aos quais se administrou placebo de amido, alem does cuidados gerais) ... [translation - control groups (six patients treated with starch placebo in addition to general care)". Comment: Method for blinding not reported, probably done but cannot be completely assured.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: Not reported, although complete case follow appears to be achieved from reporting of results.

Nikolovska 2002

Methods	RCT; two arm parallel group; open label.
Participants	80 participants; inpatient and outpatient. Inclusion criteria: Presence of clinical signs of venous ulceration (e.g. hyperpigmentation, lipodermatosclerosis, varicosities, oedema), absence of arterial insufficiency (ABI>0.85), evidence of venous insufficiency (venous refilling time determined by PPG<25 seconds). Exclusion criteria: Hypersensitivity to methylxanthines, PTX, caffeinated or cola drinks, systemic treatment with corticosteroids, cytotoxics, rutosides, anticoagulant or fibrinolytic agents with the previous 2 months, clinically significant medical conditions that would impair wound healing (renal, hepatic, haematologic, neurologic, and immunologic diseases), diabetes, infected ulcer, pregnancy or lactation, presence of ulcer for < 2 months, ulcer size < 0.75cm^2. Mean age: Gp1. 61.5 years, Gp2. 61.2 years. Mean ulcer duration: not reported. Mean ulcer size: Gp1. 5.1cm^2, Gp2. 5.4cm^2 Mean ABI: inadequate data presented.
Interventions	Group 1 (n=40): PTX 400mg tds + hydrocolloid dressing. Group 2 (n=40): hydrocolloid dressing. Treatment duration: 24 weeks
Outcomes	Complete healing: Gp1. 23/40 (58%), Gp2. 11/40 (28%). Side effects: Gp1. 11/40, Gp2. 0/40. Withdrawals: (n=14), Gp1. 5/40 (13%), Gp2. 9/40 (23%). Reasons: Side effects (Gp1. 3/40, Gp2. 0/40), infections (Gp1. 0/40, Gp2. 3/40), other medications commenced (Gp1. 1/40, Gp2. 3/40), Other (Gp1. 1/40. Gp2. 3/40)
Notes	If more than one ulcer, largest ulcer selected as reference ulcer. A priori sample size calculation. Patients were recommended compression, but refused for various reasons, including costs of bandages,

Nikolovska 2002 *(Continued)*

	discomfort whilst wearing bandages, itching, difficulties in applying bandages, and personal conviction ulcers would not heal when compressed.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The study used a prospective, randomized, open, parallel group, comparative design ...". Comment: Baseline table equivalent, but method for achieving randomisation not reported.
Allocation concealment (selection bias)	Unclear risk	Comment: Not reported.
Blinding (performance bias and detection bias) All outcomes	High risk	Quote: "The study used a prospective, randomized, open, parallel group, comparative design ...". Comment: Open label trial, so unblinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Fourteen patients were withdrawn from the trial, but they were included in the analysis as failure to heal on treatment".

Pizarro 1996

Methods	RCT: four arm parallel group; double blind.
Participants	49 participants; outpatient clinic. Inclusion criteria: Ulcer >2cm in diameter, chronic venous insufficiency determined using photoplethysmography, pneumoplethysmography and ABI. Exclusion criteria: not reported. Mean age (years): Gp1. 63, Gp2. 56, Gp3. 61, Gp4. 59. Mean ulcer duration (months): Gp1. 86, Gp2. 47, Gp3. 112, Gp4. 76. Mean ulcer size: Not reported. Mean ABI: Gp1. 1.1, Gp2. 1.0, Gp3. 0.95, Gp4. 0.9.
Interventions	Group 1 (n=12): Traditional healing (daily irrigation with 10% povidone iodine and passive dressing + single layer compression) + placebo. Group 2 (n=13): Non-traditional healing (irrigation with saline or Ringer's solution, chlorhexidine 2% and moist dressing+ single layer compression) + placebo. Group 3 (n=12): Traditional healing (daily irrigation with 10% povidone iodine and passive dressing + single layer compression) + PTX 400mg tds. Group 4 (n=12): Non-traditional healing (irrigation with saline or Ringer's solution, chlorhexidine 2% and moist dressing+ single layer compression) + PTX400mg tds. Treatment duration: three months.
Outcomes	Complete healing: Gp1. 1/12 (8%), Gp2. 5/13 (38%), Gp3. 4/12 (33%), Gp4. 7/12 (58%). Side effects: Not reported. Withdrawals: Not reported.
Notes	Healing = complete re-epithelialisation of ulcer. 60 participants recruited, but 49 analysed. Reasons for exclusion from analysis not given, nor could it be determined from which arms participants were excluded. Single layer compression (type not specified) recommended, but compliance varied between groups (Gp1. 8/12, Gp2. 11/13, Gp3. 10/12, Gp4. 11/12 compliant with compression).

Risk of bias

Pizarro 1996 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "[From English abstract] A prospective randomized double blind study with placebo group was designed ... [from text] Una vez aceptados para el estudio, se les asigno un numero randomizado que determino su entrada a los diversos grupos ... [translation] Once patients were accepted for the trial, a randomised number was assigned to them determining to which group they would belong". Comment: method for achieving randomisation not completely clear.
Allocation concealment (selection bias)	Unclear risk	Comment: Unclear as method for achieving blinding (which would generally facilitate allocation concealment if blinding organised through third party) not reported.
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "El proceso de medicion de la ulcera fue efectuado por otra Enfermera que desconocia el tipo de tratamiento indicado al paciente ... [translation] A different nurse, who did not have knowledge of the kind of treatment being applied on the patient, carried out measuring of the ulcers". Comment: Probably done, although method of double blinding not described. However, study appears at least to have blinded the outcome assessor.
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "Originalmente, el estudio se planeo para 60 pacientes, pero por diversos motivos se perdieron 11 en el curso del trabajo quedando finalmente 49, que completaron los 3 meses asignados o cicatrizaron antes ... [translation] The trial was originally planned for 60 patients; however due to several reasons 11 patients abandoned the study, meaning that finally 49 completed the set 3 months, unless healing occurred before that". Comment: 11 patients lost to follow up and excluded from the analysis.

Schürmann 1986

Methods	RCT; two arm parallel group; single blind; matching placebo.
Participants	24 participants; setting not stated. Inclusion criteria not stated. Exclusion criteria: taking vasoactive drugs. Mean ulcer size: Gp1. 5.4 cm^2, Gp2. 2.5 cm^2. No other data reported.
Interventions	Group 1: (n=12) pentoxifylline 400mg tds plus compression. Group 2: (n=12) placebo plus compression. Treatment duration: 8 weeks.
Outcomes	Healing at eight weeks: Gp1. 2/12 (16%), Gp2. 3/12 (25%). Mean reduction in ulcer size (cm^2): Gp1. 2.5, Gp2. 1.1. Side effects: Gp1. 0/12, Gp2. 2/12. Nil withdrawals.
Notes	Mean ulcer size favoured control at baseline. Type of compression not specified. Blinding not described.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Je 12 Patienten erhielten zusatzlich nach einem Randomisierungs-schema entweder Placebo (Gruppe A) oder Rentylin (Gruppe B),

Schürmann 1986 *(Continued)*

		entsprechend 1200 mg Pentoxifyllin/die ... [translation] After randomisation two groups of 12 patients received placebo (group A) or Rentylin (group B) i.e. 1200 mg pentoxifylline per day)". Comment: method for achieving randomisation not completely clear.
Allocation concealment (selection bias)	Unclear risk	Comment: Unclear as method for achieving blinding (which would generally facilitate allocation concealment if blinding organised through third party) not reported.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "[From English abstract] In a single blind controlled study..". Comment: Probably done, although method for achieving single blinding not described, nor who was blinded (e.g. patient or outcome assessor).
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: Complete case data at baseline and each treatment visit presented for each patient.

Weitgasser 1983

Methods	RCT; two arm parallel group; double blind; matching placebo.
Participants	60 participants; setting not stated. Inclusion criteria: therapy resistant ulcers of long duration; postthrombotic or varicose ulcers. Exclusion criteria not reported. Mean age: Gp1. 57 years, Gp2. 64 years. No other data reported.
Interventions	Group 1: (n=30) 400mg tds. Group 2: (n=30) placebo. Treatment duration: minimum of six weeks and maximum of eight weeks.
Outcomes	Good response (operationalised as marked healing tendency indicated by complete closure or considerable reduction in ulcer size): Gp1. 20/30 (67%), Gp2. 7/29 (24%). Side effects: Gp1. 1/30, Gp2. 0/29. Withdrawals: one. Reason: failed to attend follow-up clinic.
Notes	Sample may have included participants with co morbidities that influence outcome i.e. diabetes.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "On entry to the study, patients were allocated to 'Trental' 400 (400 mg pentoxifylline per tablet) or placebo on a random basis". Comment: method for achieving randomisation not completely clear.
Allocation concealment (selection bias)	Unclear risk	Comment: Unclear as method for achieving blinding (which would generally facilitate allocation concealment if blinding organised through third party) not reported.
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "Both preparations were made available in identical packaging without external distinguishing marks and these were numbered in a coded sequence". Comment: Achieved.
Incomplete outcome data (attrition bias)	High risk	Quote: Treatment was completed in 59 cases (30 on pentoxifylline, 29 on placebo). One female patient receiving placebo attended only one control ses-

Weitgasser 1983 *(Continued)*	
All outcomes	sion and was assessed as a drop-out ... [table 1] * 1 patient excluded from assessment". Comment: One patient excluded from analysis.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Angelides 1989	Uncontrolled open trial.
Angelides 1992	Group allocation not randomised; ulcers related to thalassaemia major not venous insufficiency.
Chodynicka 1999	Uncontrolled open trial.
de Freitas 1995	Uncontrolled open trial.
de Sanctis 2002	Not possible to determine if the participants in the trial are independent of Belcaro 2002, or a 12 month report of the same participants. Further information sought from the corresponding author, but he is unwilling to have his data contribute to a meta-analysis.
Dvorkin 1985	Uncontrolled open trial.
Galbiati 1987	Uncontrolled open trial.
Herger 1986	Uncontrolled open trial; any leg ulcer included.
Koshkin 1996	Uncontrolled open trial.
Krstic 1979	Uncontrolled open trial.
Marchitelli 1992	Conference abstract. More information required to determine if the study meets the inclusion criteria, but have not been able to locate author and no reply from letter sent to address for correspondence.
Mirshahi 1995	Outcome not meaningful to patients: physiological assay of fibrin and elastase production.
Palomares 1991	Uncontrolled open trial.
Pemler 1979	Uncontrolled open trial.
Trattner 1996	Uncontrolled open trial.
Weitgasser 1982	Uncontrolled open trial.

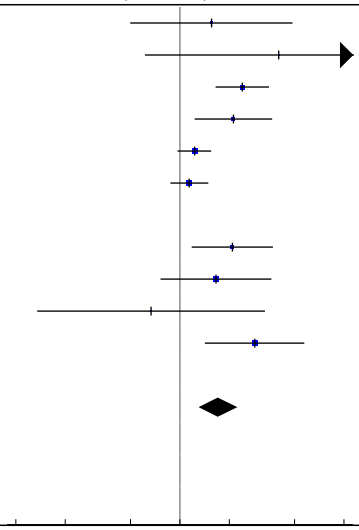
DATA AND ANALYSES

Comparison 1. 01 Pentoxifylline (Overall)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 01 Healing or significant improvement	11	841	Risk Ratio (M-H, Random, 95% CI)	1.70 [1.30, 2.24]
2 Sensitivity analysis: excluding open or single blind studies	9	737	Risk Ratio (M-H, Fixed, 95% CI)	1.60 [1.38, 1.85]
3 Sensitivity analysis: excluding trials with short treatment duration	6	693	Risk Ratio (M-H, Fixed, 95% CI)	1.55 [1.34, 1.80]
4 Sensitivity analysis: excluding trials that did not report healing only as an outcome	9	751	Risk Ratio (M-H, Fixed, 95% CI)	1.56 [1.34, 1.80]
5 Sensitivity analysis: excluding trials not using compression	7	659	Risk Ratio (M-H, Fixed, 95% CI)	1.51 [1.30, 1.76]
6 Sensitivity analysis: excluding trials that recruited hard-to-heal patients only	7	517	Risk Ratio (M-H, Fixed, 95% CI)	1.30 [1.10, 1.54]
7 Side effects	9	629	Risk Ratio (M-H, Fixed, 95% CI)	1.56 [1.10, 2.22]

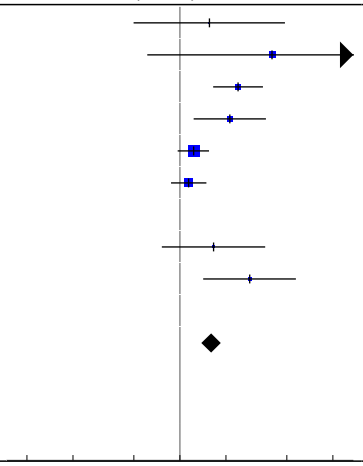
Analysis 1.1. Comparison 1 01 Pentoxifylline (Overall), Outcome 1 01 Healing or significant improvement.

Study or subgroup	Pentoxifylline n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Arenas 1988	7/18	3/12		4.53%	1.56[0.5,4.86]
Barbarino 1992	4/6	1/6		1.92%	4[0.61,26.12]
Belcaro 2002	55/84	24/88		15.26%	2.4[1.65,3.49]
Colgan 1990	23/38	12/42		11.6%	2.12[1.23,3.65]
Dale 1999	65/101	52/99		18.45%	1.23[0.97,1.55]
Falanga 1999	61/86	28/45		17.83%	1.14[0.87,1.49]
Herdy 1997	0/6	0/6			Not estimable
Nikolovska 2002	23/40	11/40		11.08%	2.09[1.18,3.69]
Pizarro 1996	11/21	6/19		7.82%	1.66[0.76,3.61]
Schürmann 1986	2/12	3/12		2.56%	0.67[0.13,3.3]
Weitgasser 1983	20/30	7/30		8.94%	2.86[1.42,5.73]
Total (95% CI)	**442**	**399**		**100%**	**1.7[1.3,2.24]**
Total events: 271 (Pentoxifylline), 147 (Control)					
Heterogeneity: Tau^2=0.09; Chi^2=22.54, df=9(P=0.01); I^2=60.07%					
Test for overall effect: Z=3.83(P=0)					



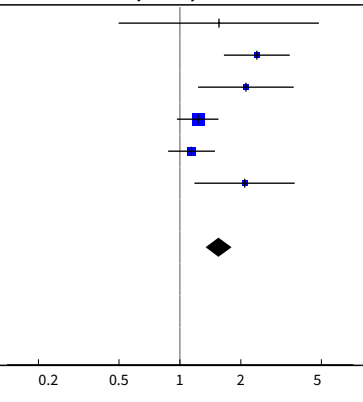
Analysis 1.2. Comparison 1 01 Pentoxifylline (Overall), Outcome 2 Sensitivity analysis: excluding open or single blind studies.

Study or subgroup	Pentoxifylline n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Arenas 1988	7/18	3/12		2.53%	1.56[0.5,4.86]
Barbarino 1992	4/6	1/6		0.7%	4[0.61,26.12]
Belcaro 2002	55/84	24/88		16.51%	2.4[1.65,3.49]
Colgan 1990	23/38	12/42		8.03%	2.12[1.23,3.65]
Dale 1999	65/101	52/99		36.98%	1.23[0.97,1.55]
Falanga 1999	61/86	28/45		25.89%	1.14[0.87,1.49]
Herdy 1997	0/6	0/6			Not estimable
Pizarro 1996	11/21	6/19		4.44%	1.66[0.76,3.61]
Weitgasser 1983	20/30	7/30		4.93%	2.86[1.42,5.73]
Total (95% CI)	**390**	**347**		**100%**	**1.6[1.38,1.85]**
Total events: 246 (Pentoxifylline), 133 (Placebo)					
Heterogeneity: Tau²=0; Chi²=20.22, df=7(P=0.01); I²=65.37%					
Test for overall effect: Z=6.17(P<0.0001)					



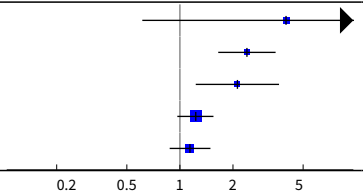
Analysis 1.3. Comparison 1 01 Pentoxifylline (Overall), Outcome 3 Sensitivity analysis: excluding trials with short treatment duration.

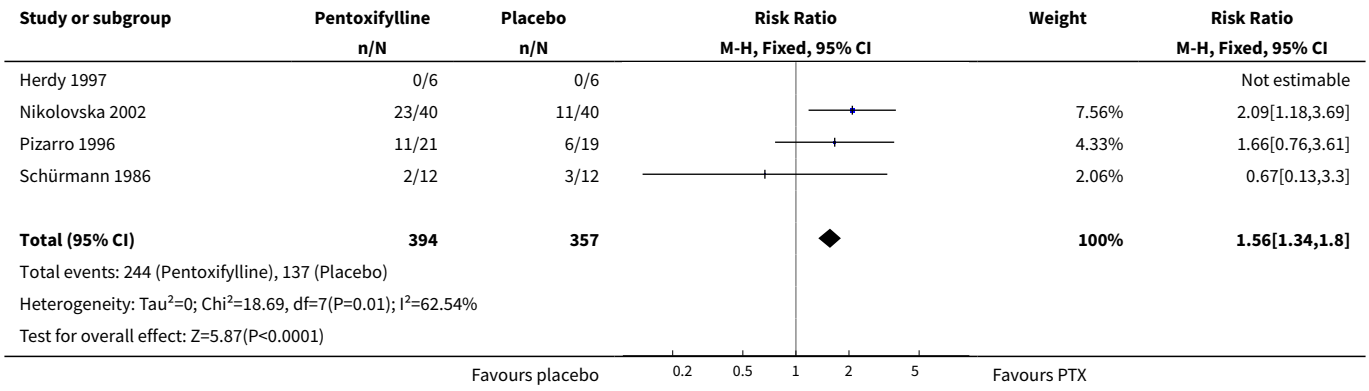
Study or subgroup	Pentoxifylline n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Arenas 1988	7/18	3/12		2.6%	1.56[0.5,4.86]
Belcaro 2002	55/84	24/88		16.9%	2.4[1.65,3.49]
Colgan 1990	23/38	12/42		8.22%	2.12[1.23,3.65]
Dale 1999	65/101	52/99		37.86%	1.23[0.97,1.55]
Falanga 1999	61/86	28/45		26.5%	1.14[0.87,1.49]
Nikolovska 2002	23/40	11/40		7.93%	2.09[1.18,3.69]
Total (95% CI)	**367**	**326**		**100%**	**1.55[1.34,1.8]**
Total events: 234 (Pentoxifylline), 130 (Placebo)					
Heterogeneity: Tau²=0; Chi²=16.56, df=5(P=0.01); I²=69.8%					
Test for overall effect: Z=5.74(P<0.0001)					



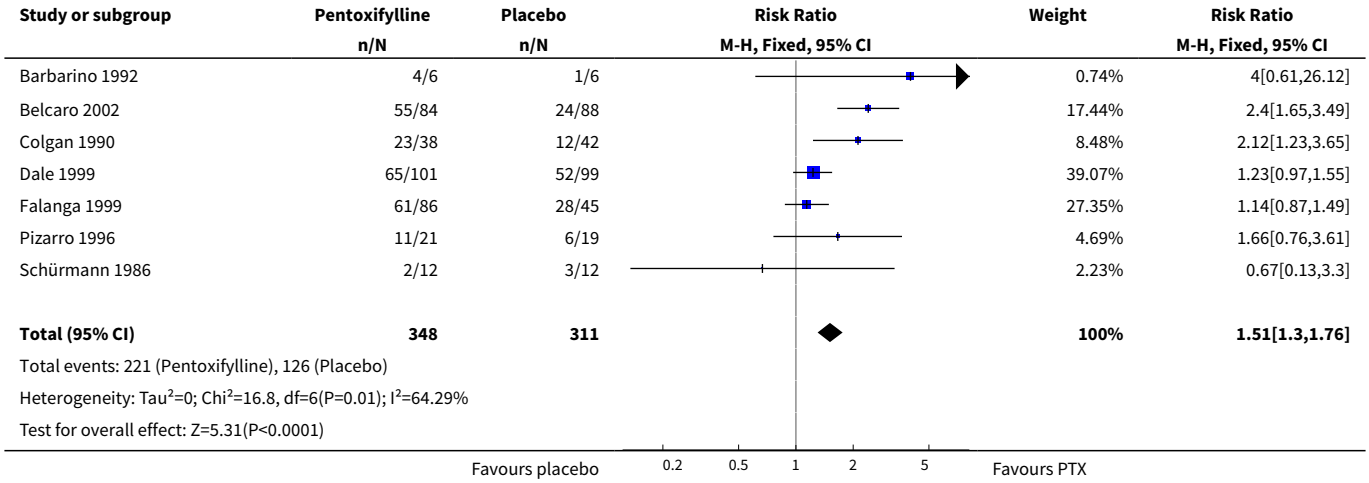
Analysis 1.4. Comparison 1 01 Pentoxifylline (Overall), Outcome 4 Sensitivity analysis: excluding trials that did not report healing only as an outcome.

Study or subgroup	Pentoxifylline n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Barbarino 1992	4/6	1/6		0.69%	4[0.61,26.12]
Belcaro 2002	55/84	24/88		16.12%	2.4[1.65,3.49]
Colgan 1990	23/38	12/42		7.84%	2.12[1.23,3.65]
Dale 1999	65/101	52/99		36.11%	1.23[0.97,1.55]
Falanga 1999	61/86	28/45		25.28%	1.14[0.87,1.49]

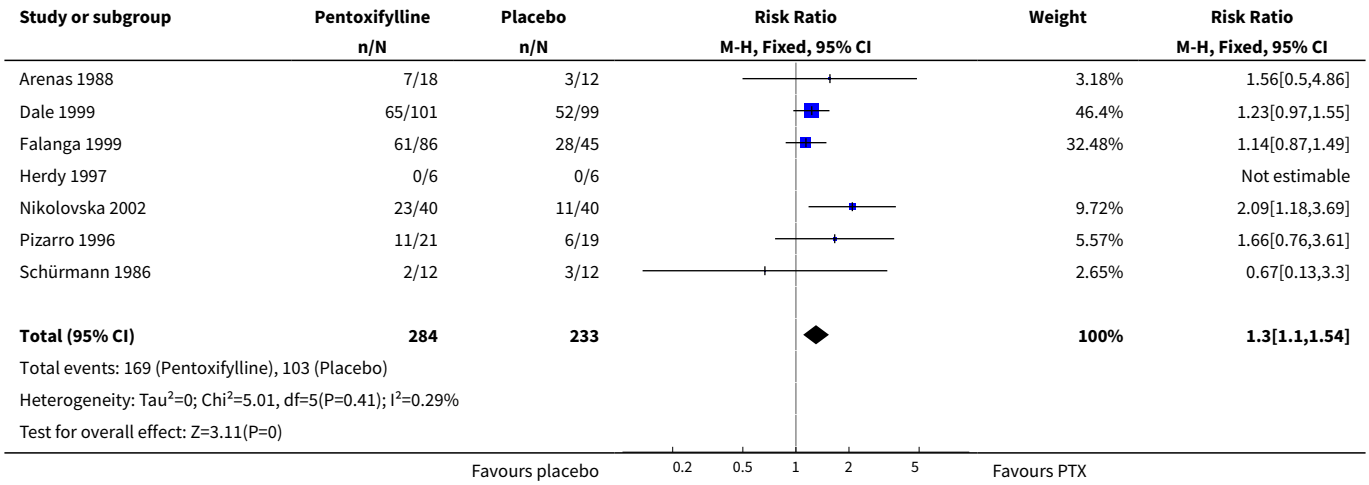




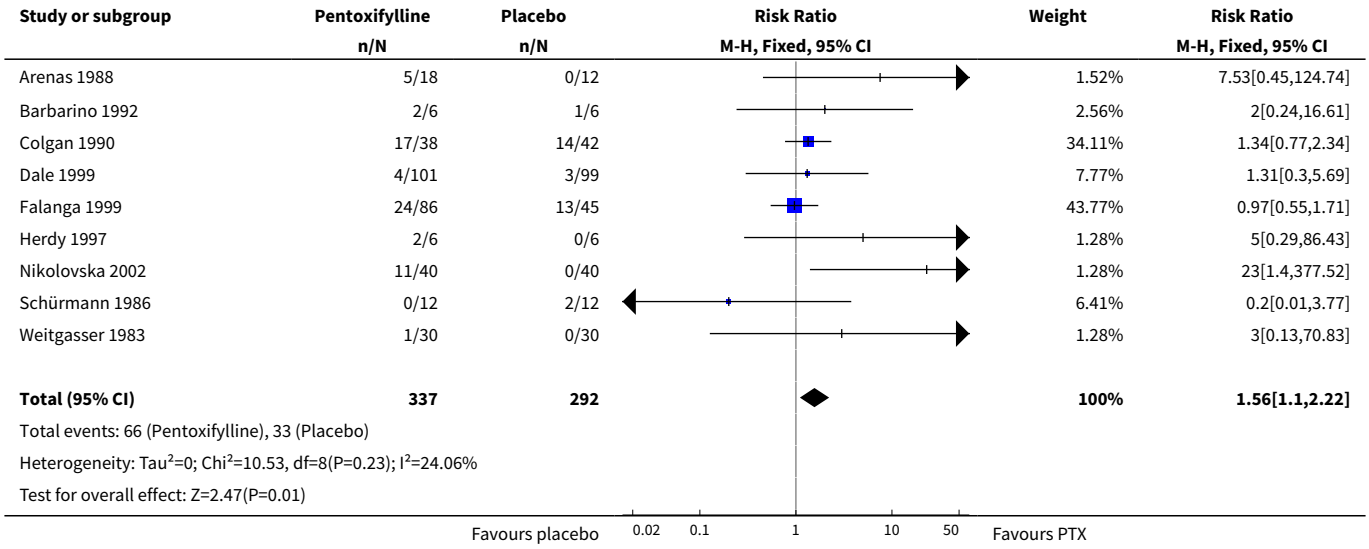
Analysis 1.5. Comparison 1 01 Pentoxifylline (Overall), Outcome 5 Sensitivity analysis: excluding trials not using compression.



Analysis 1.6. Comparison 1 01 Pentoxifylline (Overall), Outcome 6 Sensitivity analysis: excluding trials that recruited hard-to-heal patients only.



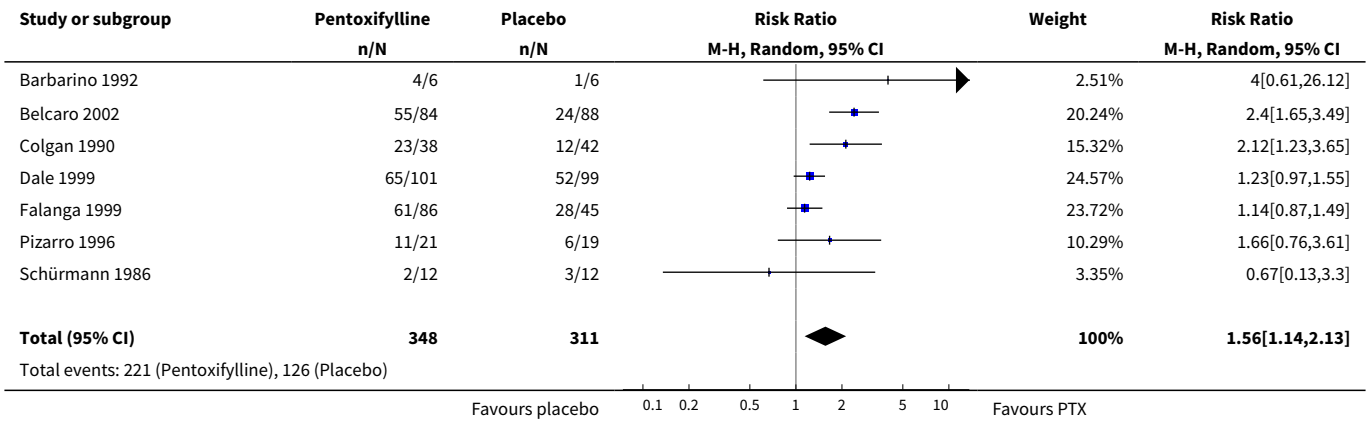
Analysis 1.7. Comparison 1 01 Pentoxifylline (Overall), Outcome 7 Side effects.

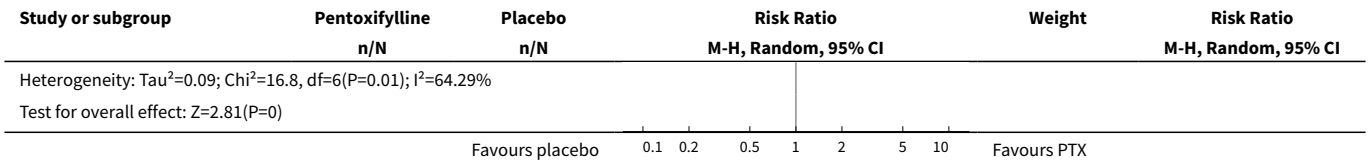


Comparison 2. 02 Pentoxifylline with compression

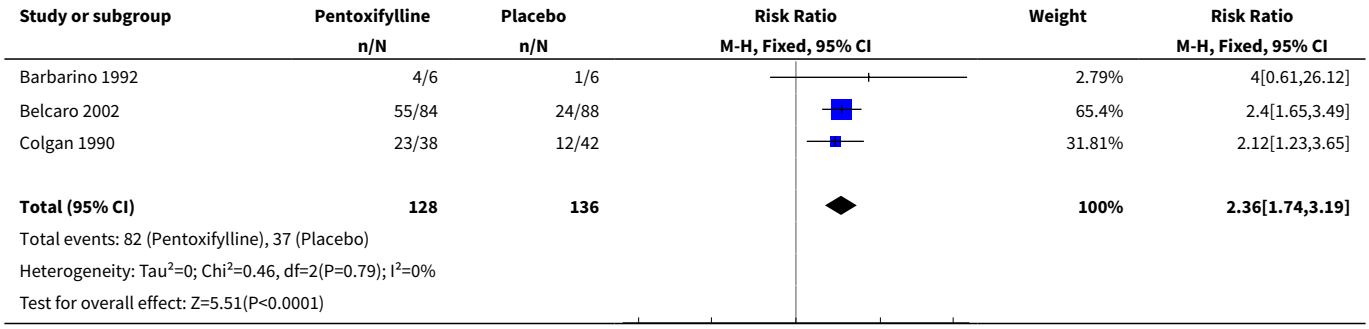
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 01 Complete healing	7	659	Risk Ratio (M-H, Random, 95% CI)	1.56 [1.14, 2.13]
2 01 Sensitivity analysis: hard-to-heal patients	3	264	Risk Ratio (M-H, Fixed, 95% CI)	2.36 [1.74, 3.19]
3 Sensitivity analysis: normal healing patients	4	395	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [1.01, 1.43]

Analysis 2.1. Comparison 2 02 Pentoxifylline with compression, Outcome 1 01 Complete healing.

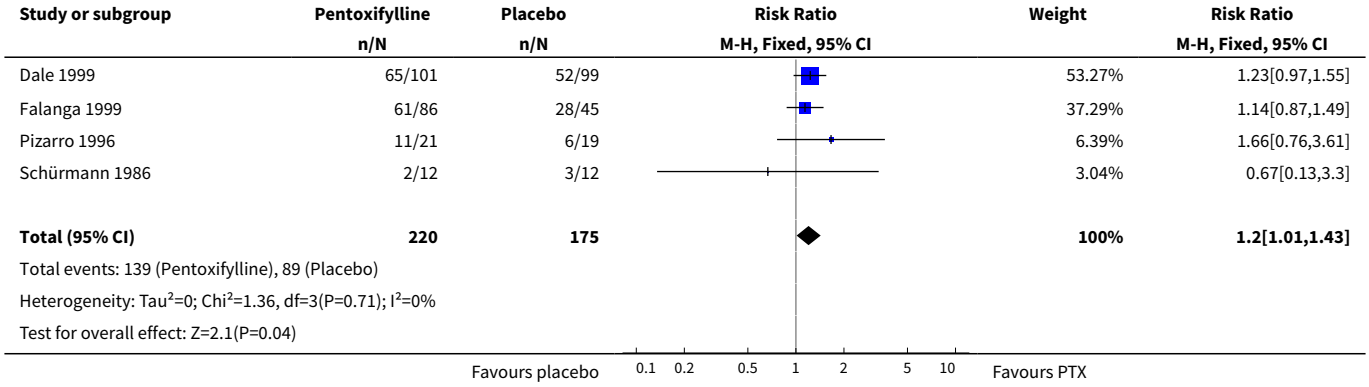




Analysis 2.2. Comparison 2 02 Pentoxifylline with compression, Outcome 2 01 Sensitivity analysis: hard-to-heal patients.



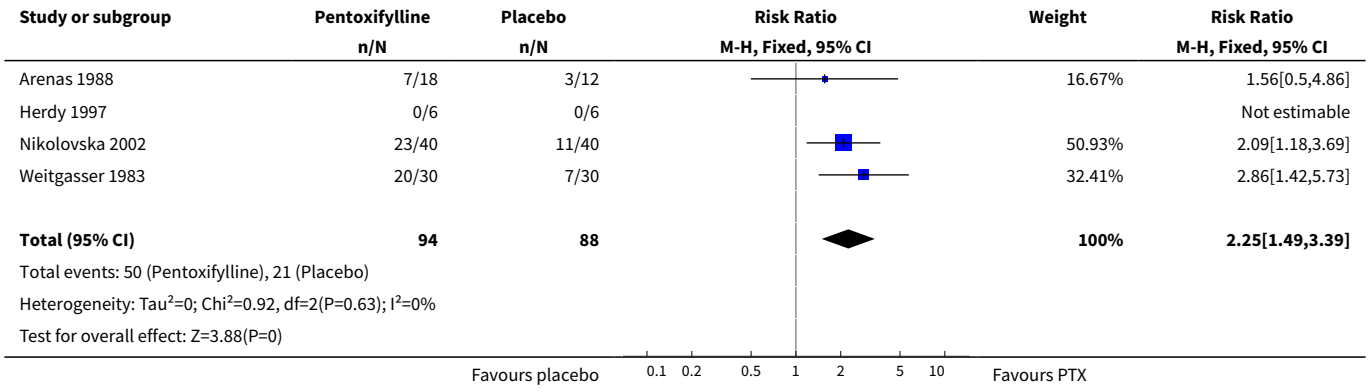
Analysis 2.3. Comparison 2 02 Pentoxifylline with compression, Outcome 3 Sensitivity analysis: normal healing patients.



Comparison 3. 03 Pentoxifylline without compression

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 01 Complete healing or significant improvement	4	182	Risk Ratio (M-H, Fixed, 95% CI)	2.25 [1.49, 3.39]

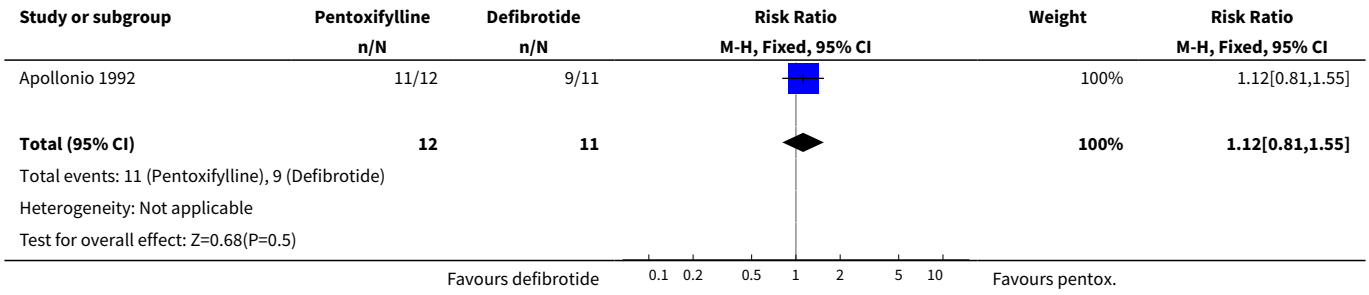
Analysis 3.1. Comparison 3 03 Pentoxifylline without compression, Outcome 1 01 Complete healing or significant improvement.



Comparison 4. 04 Pentoxifylline vs defibrotide

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 01 Complete healing at 3 months	1	23	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.81, 1.55]

Analysis 4.1. Comparison 4 04 Pentoxifylline vs defibrotide, Outcome 1 01 Complete healing at 3 months.



ADDITIONAL TABLES

Table 1. Quality assessment by trial

Trial ID: pts / arm	Incl / excl criteria	Power calc.	Randomisation	Allocation concealed	Baseline equivalence	Blinding	Outcomes	ITT Analysis
Weitgasser 1983: 60 pts in two arms	Yes / No	Not reported	Method not reported	Unclear	Comparable for age and sex, but no other data reported	Double	Appropriate (healing response operationally defined as good, satisfactory, no change or worse	No - one pt withdrew and was excluded from the analysis
Schürmann 1986: 24 pts in 2 arms	No / Yes	Not reported	Method not reported	Unclear	Mean ulcer size favoured control group. Other information reported	Single	Appropriate (ulcer size at baseline and trial completion reported	Not reported - no withdrawals
Arenas 1988: 30 pts in 2 arms	No / Yes	Not reported	Method not reported	Unclear	Not reported	Double	Appropriate (healing response operationally defined as healing & significant improvement, improvement, no change or worse	No - five pts withdrew and were excluded from the analysis
Colgan 1990: 80 pts in 2 arms	Yes / No	Not reported	Randomisation by balanced blocks of eight in separate lists for each centre	Unclear	Yes	Double	Appropriate - numbers of ulcers healed	Not reported but withdrawals included in results as treatment failures
Apollonio 1992	Yes / Yes	Not reported	Method not reported	Unclear	Yes	Not reported	Appropriate - numbers of ulcers healed	Not reported but no withdrawals
Barbarino 1992: 12 pts in 2 arms	Yes / Yes	Not reported	Method not reported	Unclear	Yes	Double	Appropriate - ulcer size at baseline and trial conclusion reported	Not reported but no withdrawals

Table 1. Quality assessment by trial *(Continued)*

Pizarro 1996: 60 pts in 4 arms	Yes / No	Not reported	Method not reported	Unclear	Mean ulcer duration and ABI favoured control group	Double	Appropriate - number of ulcers healed	No - 11 pts excluded, but not reported from which groups
Herdy 1997: 12 pts in 2 arms	Yes / Yes	Not reported	Method not reported	Unclear	Mean ulcer size favoured control group and mean ulcer duration favoured PTX group	Not reported	Appropriate - ulcer size at baseline and trial completion	Not reported, but no withdrawals
Dale 1999: 200 pts in 2 arms within a factorial trial	Yes / Yes	Yes	Sequential sealed envelopes	Adequate	Yes	Double	Appropriate - numbers of ulcers healed	Yes
Falanga 1999: 131 pts in 3 arms	Yes / Yes	Yes	Method of randomisation not reported	Adequate: randomisation by pharmaceutical company	Mean ulcer size favoured PTX 2400mg and placebo groups	Double	Appropriate - numbers of ulcers healed (but numbers extrapolated from life analysis table)	No - 2 pts excluded
Belcaro 2002: 172 pts in 2 arms	Yes / Yes	Not reported	Method not reported but followed same method as Colgan	Unclear	Yes	Double	Appropriate - numbers of ulcers healed	No - 12 pts excluded from the analysis
Nikolovska 2002: 80 pts in 2 arms	Yes / Yes	Yes	Method not reported	Unclear	Yes	Open label	Appropriate - numbers of ulcers healed	Not reported but withdrawals included in analysis

APPENDICES

Appendix 1. Search strategy - fourth update 2010

For this fourth update we searched the following electronic databases:

Cochrane Wounds Group Specialised Register (Searched 13/5/09);
The Cochrane Central Register of Controlled Trials (CENTRAL) - The Cochrane Library Issue 2 2009;
Ovid MEDLINE - 1950 to May Week 1 2009;
Ovid EMBASE - 1980 to 2009 Week 19;
Ovid CINAHL - 1982 to May Week 2 2009.

The following search strategy was used in The Cochrane Central Register of Controlled Trials (CENTRAL):
#1 MeSH descriptor Leg Ulcer explode all trees
#2 (varicose NEXT ulcer*) or (venous NEXT ulcer*) or (leg NEXT ulcer*) or (foot NEXT ulcer*) or (stasis NEXT ulcer*) or ((lower NEXT extremit*) NEAR/2 ulcer*):ti,ab,kw
#3 (#1 OR #2)
#4 MeSH descriptor Pentoxifylline explode all trees
#5 pentoxifylline or oxpentifylline
#6 trental or torental or techlon or tarontal or sipental or hemovas or harine or felxital or elorgan or ebisan or ceretal or azupentat or artal
#7 (#4 OR #5 OR #6)
#8 (#3 AND #7)

The search strategies for Ovid MEDLINE, Ovid EMBASE and Ovid CINAHL can be found in Appendix 2, Appendix 3 and Appendix 4 respectively. The Ovid MEDLINE search was combined with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision); Ovid format. The EMBASE and CINAHL searches were combined with the trial filters developed by the Scottish Intercollegiate Guidelines Network (SIGN). We did not apply any date or language restrictions.

Appendix 2. Ovid MEDLINE search strategy

1 exp Leg Ulcer/
2 (varicose ulcer* or venous ulcer* or leg ulcer* or foot ulcer* or (feet adj ulcer*) or stasis ulcer* or (lower extremit* adj ulcer*) or crural ulcer* or ulcus cruris).ti,ab.
3 or/1-2
4 exp Pentoxifylline/
5 (pentoxifylline or oxpentifylline).ti,ab.
6 (trental or torental or techlon or tarontal or sipental or hemovas or harine or felxital or elorgan or ebisan or ceretal or azupentat or artal).ti,ab. (312)
7 or/4-6
8 3 and 7

Appendix 3. Ovid EMBASE search strategy

1 exp Leg Ulcer/
2 (varicose ulcer* or venous ulcer* or leg ulcer* or foot ulcer* or (feet adj ulcer*) or stasis ulcer* or (lower extremit* adj ulcer*) or crural ulcer* or ulcus cruris).ti,ab.
3 or/1-2
4 exp Pentoxifylline/
5 (pentoxifylline or oxpentifylline).ti,ab.
6 (trental or torental or techlon or tarontal or sipental or hemovas or harine or felxital or elorgan or ebisan or ceretal or azupentat or artal).ti,ab. (182)
7 or/4-6
8 3 and 7

Appendix 4. EBSCO CINAHL search strategy

S9 S4 and S8
S8 S5 or S6 or S7
S7 TI (trental or torental or techlon or tarontal or sipental or hemovas or harine or felxital or elorgan or ebisan or ceretal or azupentat or artal) or AB (trental or torental or techlon or tarontal or sipental or hemovas or harine or felxital or elorgan or ebisan or ceretal or azupentat or artal)
S6 TI (pentoxifylline or oxpentifylline) or AB (pentoxifylline or oxpentifylline)
S5 (MH "Pentoxifylline")

S4 S1 or S2 or S3
S3 TI (lower extremit* and ulcer*) or AB (lower extremit* and ulcer*)
S2 TI (varicose ulcer* or venous ulcer* or leg ulcer* or foot ulcer* or stasis ulcer* or crural ulcer* or ulcus cruris) or AB (varicose ulcer* or venous ulcer* or leg ulcer* or foot ulcer* or stasis ulcer* or crural ulcer* or ulcus cruris)
S1 (MH "Leg Ulcer+")

Appendix 5. Criteria for a judgment of 'yes' for the sources of bias

1. Was the allocation sequence randomly generated?

low risk of bias

The investigators describe a random component in the sequence generation process such as: referring to a random number table; using a computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots.

high risk of bias

The investigators describe a non-random component in the sequence generation process. Usually, the description would involve some systematic, non-random approach, for example: sequence generated by odd or even date of birth; sequence generated by some rule based on date (or day) of admission; sequence generated by some rule based on hospital or clinic record number.

Unclear

Insufficient information about the sequence generation process to permit judgement of 'Yes' or 'No'.

2. Was the treatment allocation adequately concealed?

low risk of bias

Participants and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation: central allocation (including telephone, web-based and pharmacy-controlled randomisation); sequentially-numbered drug containers of identical appearance; sequentially-numbered, opaque, sealed envelopes.

high risk of bias

Participants or investigators enrolling participants could possibly foresee assignments and thus introduce selection bias, such as allocation based on: using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure.

Unclear

Insufficient information to permit judgement of 'Yes' or 'No'. This is usually the case if the method of concealment is not described or not described in sufficient detail to allow a definite judgement, for example if the use of assignment envelopes is described, but it remains unclear whether envelopes were sequentially numbered, opaque and sealed.

3. Blinding was knowledge of the allocated interventions adequately prevented during the study?

low risk of bias

Any one of the following:

- No blinding, but the review authors judge that the outcome and the outcome measurement are not likely to be influenced by lack of blinding.
- Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
- Either participants or some key study personnel were not blinded, but outcome assessment was blinded and the non-blinding of others unlikely to introduce bias

high risk of bias

Any one of the following:

- No blinding or incomplete blinding, and the outcome or outcome measurement is likely to be influenced by lack of blinding.
- Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken.
- Either participants or some key study personnel were not blinded, and the non-blinding of others likely to introduce bias.

Unclear

Any one of the following:

- Insufficient information to permit judgement of 'Yes' or 'No'.
- The study did not address this outcome.

4. Were incomplete outcome data adequately addressed?

low risk of bias

Any one of the following:

- No missing outcome data.
- Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias).
- Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups.
- For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate.
- For continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size.
- Missing data have been imputed using appropriate methods.

high risk of bias

Any one of the following:

- Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups.
- For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate.
- For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size.
- 'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation.
- Potentially inappropriate application of simple imputation.

Unclear

Any one of the following:

- Insufficient reporting of attrition/exclusions to permit judgement of 'Yes' or 'No' (e.g. number randomized not stated, no reasons for missing data provided).
- The study did not address this outcome.

WHAT'S NEW

Date	Event	Description
25 October 2012	New search has been performed	New search, no additional studies identified.
25 October 2012	New citation required but conclusions have not changed	Fifth update, no change to conclusions.

HISTORY

Protocol first published: Issue 2, 1999
Review first published: Issue 1, 2000

Date	Event	Description
7 December 2010	New search has been performed	New search, no additional studies identified, no change to conclusions.

Date	Event	Description
11 August 2009	Amended	Contact details updated.
13 March 2009	New search has been performed	New search, no new studies identified; two studies previously awaiting assessment now added to the table of Excluded studies (n= 16). No change to conclusions.
3 September 2008	Amended	Converted to new review format.
5 April 2007	New citation required and conclusions have changed	Substantive amendment. For this second update, published in the Cochrane Library, Issue 3, 2007, new searches were carried out in (February 2007). 5 new studies identified, 3 were included in this review (Pizarro, Belcaro and Nikolovska). We are awaiting further information on 2 studies (De Sanctis and Marchitelli). We have received information about a possible negative trial that remains unpublished (possibly called the PRIDE study). However, further inquiries to the sources of this information have retrieved no additional details to assist in locating the study and a search of the manufacturer's database (including conference presentations) has not identified any such trial. Five additional studies were added to the Table of Excluded studies (n= 14).
4 April 2001	New citation required and conclusions have changed	For this first update new searches were carried out in (April 2001). 14 citations to 9 studies were included in the review. 7 additional studies were excluded (total n = 9) including trials by Galbiati (Italian language) and Chodynicka (Polish language). We have added a table summarising sensitivity analyses performed to assess the robustness of the results to the exclusion of particular trials. The first update of this review was published in the Cochrane Library, Issue 1, 2002.

CONTRIBUTIONS OF AUTHORS

AJ and BA identified studies from the initial search and selected studies for data extraction. AJ extracted the data from studies and this was independently reviewed for accuracy by JW. AJ synthesized the extracted data and drafted the report. VP conducted analyses testing for publication bias. VP, BA and JW reviewed the report. AJ coordinated the updated of the review and is the guarantor of the review.

Contributions of editorial base:

Nicky Cullum: edited the review, advised on methodology, interpretation and review content. Approved the final review prior to submission.
Sally Bell-Syer: coordinated the editorial process. Advised on methodology, interpretation and content. Edited and copy edited the review and the updated review.
Ruth Foxlee: designed the search strategy, ran the searches and edited the search methods section for the update.

DECLARATIONS OF INTEREST

Andrew B Jull, Varsha Parag and Jill Waters - none known.
Bruce Arroll - is on the advisory board for the educational seminars run by Pharmac, New Zealand's government funded drug purchasing agency. He is also on the primary care committee of the Future Forum and educational foundation funded by Astra Zeneca (UK). He has also accepted travel and conference funding from Sanofi Aventis.

SOURCES OF SUPPORT

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- Dept of General Practice & Primary Care, University of Auckland, New Zealand.
- Auckland Healthcare Services, New Zealand.

External sources

- NIHR/Department of Health (England), (Cochrane Wounds Group), UK.

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Oral; Bandages; Combined Modality Therapy [methods]; Fibrinolytic Agents [therapeutic use]; Leg Ulcer [*drug therapy] [therapy]; Pentoxifylline [adverse effects] [*therapeutic use]; Polydeoxyribonucleotides [therapeutic use]; Randomized Controlled Trials as Topic; Vasodilator Agents [adverse effects] [*therapeutic use]

MeSH check words

Humans